

**REMARKS**

The rejection has been considered at length. However, for the reasons set forth below it is submitted that the claimed subject matter would not have been rendered obvious by the combination of the cited references.

Claims 1, 3-7, 9, 11-14, 18-39 are pending and have been examined on the merits.

Claims 1, 3-7, 9, 11-14, 18-39 have been rejected under 35 U.S.C. § 103(a) as being obvious over Rusckowski et al (Journal of Nuclear Medicine, 1996, Vol. 37, pages 1655-1662, hereinafter "Rusckowski") or Samuel et al., (Journal of Nuclear Medicine, 1996, Vol. 37, pages 55-61, hereinafter "Samuel") in view of Goldenberg (U.S. Patent Application Publication No. 2001/0006618, hereinafter "Goldenberg") Cokgor et al. (Journal of Clinical Oncology, 2000, Vol. 18, pages 3862-3872, hereinafter "Cokgor"); and MacPhee et al. (U.S. Patent No. 6,054,122, hereinafter "MacPhee").

Applicants respectfully traverse.

Applicants wish to incorporate by references the previously filed responses. In addition, Applicants wish to provide the following additional comments.

As submitted in the previous response, the presently claimed invention is directed to a method of treating a patient with solid tumor by first administering intraoperatively a first agent as avidin, streptavidin, etc and then administering postoperatively a second anticancer agent having affinity for the first agent (*e.g.*, page 8, lines 12-15 and lines 17-24). Because avidin is endowed with tumor tropism, the presently claimed invention can be successfully used on tumors which do not express antigens (*e.g.*, page 8).

Rusckowski does not disclose Applicants' invention. Rusckowski only provides for a method for imaging osteomyelitis (an infection of the bones) with streptavidin and biotin (*e.g.*,

the abstract). Rusckowski also discloses that first, unlabelled streptavidin was administered and allowed to accumulate nonspecifically into the lesion, probably in a manner similar to polyclonal IgG, then, the radiolabel was delivered bound to biotin (*e.g.*, page 1655, right col, lines 12-16). Further, Rusckowski discloses that biotin alone is also very successful in detecting infected lesions (*e.g.*, page 1659, right col., first paragraph).

Samuel also does not disclose Applicants' invention. Samuel describes a method to detect infections (prosthetic vascular graft infection) by i.v. injection of unlabelled streptavidin followed by labeled biotin (*e.g.*, page 55, left col, first paragraph and right col., second full paragraph). Samuel also, as Rusckowski above, discloses that unlabeled avidin is a protein which accumulates non-specifically at sites of inflammations (*e.g.*, page 55, right col., second full paragraph). As such, neither Rusckowski nor Samuel discloses, teaches or even suggests the presently claimed method of treating a patient with solid tumor by first administering intraoperatively a first agent as avidin, streptavidin, etc and then administering postoperatively a second anticancer agent having affinity for the first.

As previously submitted, Goldenberg only provides for a method for injecting a patient with a first composition comprising either streptavidin- or avidin-conjugated antibody, biotinylated antibody to be used in conjunction with avidin and biotin...wherein the antibody is an antibody or an antibody fragment which specifically binds a marker produced by or associated with the lesion (*e.g.*, page 1, paragraph [0003], page 3 paragraph [0036]). As also previously submitted, the first composition of Applicants' invention does not contain a monoclonal antibody and the affinity for the tumor is provided by avidin only.

Cokgor does not provide for the missing links in that it suffers from the same defects. Cokgor also discloses the administration of I-131 labeled antibody administered into surgically

created resection cavities in patients suffering from malignant gliomas (*e.g.*, the abstract). As such, the combination of Rusckowski or Samuel with Goldenberg and Cokgor still is not the presently claimed invention.

MacPhee also does not add anything to the combination of Rusckowski or Samuel with Goldenberg and Cokgor. MacPhee only discloses a fibrin sealant dressing which could be supplemented with a number of drugs to prevent infections, inflammations etc (*e.g.*, the abstract).

Therefore, one of ordinary skill in the art would not have received any guidance from MacPhee to administer a first agent selected from the group consisting of only avidin, streptavidin etc.

Thus, Applicants assert that Rusckowski or Samuel do not provide the missing link to the combination of Goldenberg, Cokgor and MacPhee. Both Rusckowski and Samuel are completely silent with regard to solid tumors or to administration of streptavidin with specific tropism for the tumors. Thus, none of them provide any motivation for using streptavidin as an agent endowed with tumor tropism. On the contrary, they teach away from the presently claimed invention in that they both described that avidin accumulates non-specifically at the sites of inflammation and Rusckowski reports that biotin alone works as well as streptavidin. Thus, the teachings of Rusckowski and Samuel are in synchrony with Goldenberg and Cokgor which teach to combine streptavidin with antibodies to provide for the lack of specificity.

As such, the Examiner's asserted combination does not render obvious the subject matter of claims 1, 3-7, 9, 11-14, 18-39 to one skilled in the art.

Thus, withdrawal of the rejection of the claims under 35 C.F.R. § 103(a) is respectfully requested.

This response is being filed within shortened statutory period for response. Thus, no

further fees are believed to be required. If, on the other hand, it is determined that any further fees are due or any overpayment has been made, the Assistant Commissioner is hereby authorized to debit or credit such sum to Deposit Account No. 02-2275.

Pursuant to 37 C.F.R. 1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. The fee associated therewith is to be charged to Deposit Account No. 02-2275.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,  
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